EPA Reviewer: Christopher Schlosser, M.F.S **Signature:** _____
Risk Assessment Branch VI, Health Effects Division (7509P) **Date:** _____
EPA Secondary Reviewer: Yung G. Yang, Ph.D. **Signature:** _____
Risk Assessment Branch VI, Health Effects Division (7509P) **Date:** _____

Template version 09/11

TXR#: 0056765

DATA EVALUATION RECORD[1]

STUDY TYPE: 90-Day Oral Toxicity Feeding - Rat; OPPTS 870.3100 [§82-1a]; OECD 408.

PC CODE: 016331 **DP BARCODE:** D410187

TEST MATERIAL (PURITY): Momfluorothrin (95.7% a.i.)

SYNONYMS: S-1563

CITATION: Sommer, E.W. (2011) Repeated Dose Oral (Feeding) Toxicity Study in the Wistar Rat followed by a 6-Week Recovery. Harlan Laboratories Ltd. Itingen, Switzerland. C37995, October 18, 2011. MRID 49020006. Unpublished.

SPONSOR: Sumitomo Chemical Company, Ltd.

EXECUTIVE SUMMARY:

In a 90-day oral toxicity study (MRID 49020006), S-1563 (Momfluorothrin, 95.7% a.i./Batch #9CM0109G) was administered to Wistar rats (12/sex/dose), with additional 6-week recovery groups in the control and high-dose groups (6/sex/dose), in the diet at dose levels of 0, 300, 1000, 3000, and 6000 ppm (equivalent to 0, 23, 76, 223, and 485 mg/kg bw/day in males and 0, 25, 82, 236, and 500 mg/kg in females).

No mortality, treatment-related clinical signs, or neurological effects were identified under the tested conditions. S-1563 caused a slight but significant decrease in body weights at 3,000 and 6,000 ppm in both males and females. Body weight remained decreased following the 42-day recovery period, however, slight improvement in body weight gain was observed in both sexes.

In females, a slight but statistically significant decrease in hemoglobin and decreased PTT were reported at 3000 and 6000 ppm, along with slightly decreased MCV and MCH in the high-dose group. Additionally, increases in lymphocytes and large unstained cells (LUC) were reported in the high-dose group. All hematological findings were reversed following the 6-week recovery period.

Treatment-related increases in clinical chemistry parameters included: total plasma cholesterol, and phospholipids in males and females treated at 1000, 3000 and 6000 ppm; triglycerides in males and females at 6000 ppm only; GGT in males and females at 3000 and 6000 ppm; total

1 Disclaimer: The attached Data Evaluation Record is a modified version of the Tier II Summary provided by Sumitomo Chemical Co. Ltd. Portions of this document may have been altered by the EPA reviewer.

protein content and alpha-2 globulin fraction in males at 1000, 3000 and 6000 ppm; albumin in males and females at 3000 and 6000 ppm; and alanine aminotransferase (ALT) was minimally increased in females at 6000 ppm.

The only macroscopic finding that was considered to be related to treatment was enlarged liver, reported among males at 3000 and 6000 ppm. Mean liver weights were increased in males at 3000 and 6000 ppm by 25%, and 57%, respectively, and in females at 6000 ppm by 37%. Relative liver weights were increased in males at 3000 and 6000 ppm by 44%, and 78%, respectively, and in females at 3000 and 6000 ppm by 27% and 46%, respectively.

Histological examination of the liver revealed intracellular depositions of a brown pigment among males and females receiving 1000, 3000 or 6000 ppm, and bile duct proliferation and minor degrees of diffuse hepatocellular hypertrophy were also observed in males at 3000 and 6000 ppm, and females at 6000 ppm. Other histological changes included brown pigment in the kidney and diffuse acinar hypertrophy in mandibular salivary glands observed at 3000 and 6000 ppm.

Following 90-days of administration of S-1563 to Wistar rats, the liver was the primary target organ. Increases in lipids, proteins, and GGT were identified along with enlarged livers, increases in liver weights, diffuse hepatocellular hypertrophy and bile duct proliferation.

The systemic toxicity LOAEL for this study is 3,000 ppm (223/236 mg/kg/day) based on decreased body weights, increases in liver enzyme activity, lipids, protein, liver weights, diffuse hepatocellular hypertrophy and bile duct proliferation. The systemic toxicity NOAEL is 1,000 ppm (76/82 mg/kg/day).

***Note: PMRA agrees with the study author and considers the decrease in body weight gain in females at 1000 ppm (76/82 mg/kg bw/day) to be toxicologically relevant. Therefore, the PMRA considers the NOAEL to be 23/25 mg/kg bw/day, and the LOAEL to be 76/82 mg/kg bw/day**.

This 90-day oral toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study OPPTS 870.3100; OECD 408) in rats. The lack of stability data was noted as a minor deficiency. However, this is not expected to impact the results of the study.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test Material S-1563, (Momfluorothrin)
Description: White solid
Lot/Batch: 9CM0109G
Purity: 95.7%
CAS#: 609346-29-4
Stability: Cited to be "stable under storage conditions"

2. Vehicle Basal diet. Water was added as an aid to pelleting.

3. Test Animals
Species Rat
Strain Wistar (HanRcc:WIST (SPF))
Age Approximately 6 weeks old at start of treatment
Weight 129.5 – 179.7 g (males), 106.5 – 139.2 g (females) at administration
Source Harlan Laboratory Animal Services, Fuellinsdorf, Switzerland.
Acclimation period 7 days
Diet Pelleted standard Kliba 3433 rodent maintenance diet (Provim Kliba SA, Switzerland)
Water Tap water *ad libitum*
Housing In groups of three in Makrolon type-4 cages with wire mesh tops and sterilized standard softwood bedding.

Environmental conditions
Temperature 22 ± 3ºC with the exception of:
19 ± 3ºC (25 May 2009 – 8 July 2009)
Humidity 30-70%
Air change 10-15 air changes per hour
Photoperiod 12 hour light / dark cycle

B. STUDY DESIGN:

1. In life dates: 26 May 2009 – 6 October 2009

2. Animal assignment: Animals were assigned by weight stratification, not exceeding ±20% of the mean weight of each sex, to the test groups noted in Table 1.

TABLE 1: Study design

Test group	Conc. in died (ppm)	Dose to animal (mg/kg/day)(M/F)	# Male	# Female
Control	0		18 (12 main, 6 recovery)	18 (12 main, 6 recovery)
Low	300	23/25	12	12
Mid-Low	1,000	76/82	12	12

Test group	Conc. in died (ppm)	Dose to animal (mg/kg/day)(M/F)	# Male	# Female
Mid-High	3,000	223/236	12	12
High	6,000	485/500	18 (12 main, 6 recovery)	18 (12 main, 6 recovery)

3. **Dose selection rationale:** The dose levels are based on a 13-Week repeated dose oral toxicity (feeding) study in the Wistar rat, performed at Harlan Laboratories Ltd. (RCC study no. B57936) using dose levels of 300, 1000, 3000 and 6000 ppm. Animals treated with 3000 and 6000 ppm were expected to show treatment-related effects on body weight gain and in the liver.

4. **Diet preparation and analysis:** Dietary admixtures (Pelleted standard Kliba 3433 rodent maintenance diet, were prepared weekly during the first five study weeks and then every two weeks. S-1563 was weighed into a tared glass beaker on a suitable precision balance, and mixed with microgranulated feed separately for each dose group. An appropriate amount of water was added to aid pelleting. The pellets were dried with air for at least 48 hours before storage. Control feed was prepared similarly, but without test item. Feed preparations were stored in the refrigerator until use.

   Fifty gram samples from each the top, middle and bottom from all diet preparations (including controls) were taken and dispatched to the responsible authority for analytical chemistry. The samples were frozen in the analytical laboratory and stored at -20 ± 5 °C until analysis. Samples of the diet preparations for weeks 6 and 8 were erroneously not collected. Analysis was by GC-FID.

Results:

Homogeneity analysis (%RSD): 0.2 to 11.6

Stability analysis (% Initial): The study report stated that stability of the test item was verified for 24 hours at room temperature under artificial light conditions, for up to 28 days at room temperature in the dark, and for up to 28 days in the refrigerator or deep freezer in the dark (data not provided).

Concentration analysis (% Nominal): 80.9 to 109.8

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** All analyses were two-tailed for significance levels of 5% and 1%. If the variances were clearly heterogeneous, appropriate transformations (e.g. log, square root, double arcsine) were used in an attempt to stabilize the variances. For quantitative data: Body weights, body weight gain, food consumption, clinical pathology values (hematology, clinical biochemistry), and absolute organ weights were analyzed initially by a one-way analysis of variance (ANOVA). Organ weights were also analyzed by analysis of covariance (ANCOVA) on final body weight. Summary values of organ to body weight ratios were analyzed statistically. For all of the parameters evaluated initially by ANOVA or ANCOVA, Dunnett's test was used to

compare the control and treated groups, based on the error mean square in the ANOVA or ANCOVA. The Dunnett's test was performed for all continuous data parameters, regardless of whether the initial ANOVA or ANCOVA was statistically significant, and statistical flags were presented in the tables of results in the final report. Ophthalmoscopy, macropathology and histopathology data were analyzed using the one-sided Fisher's Exact Test. The Steel test was applied instead of Dunnett's test when the data could not be assumed to follow a normal distribution. For qualitative data (e.g. possible values of 0, 1, 2 or present/absent): Qualitative functional observational battery parameters were not analyzed statistically. Parameters from urine analysis were evaluated using the Steel test as data cannot be assumed to follow a normal distribution. Individual values were rounded before printing. All derived values that appear in the report tables represent the rounded results of calculations that are based on the exact (non-rounded) raw data values. Statistical analyses were also carried out on the exact raw data values.

C. METHODS:

1. Observations:

1a. Cageside observations: All animals were observed twice a day for viability and mortality.

1b. Clinical examinations: General clinical observations were made once daily during the acclimatization, treatment and recovery periods. Detailed observations were made weekly in the acclimatization period and during weeks 1 to 12 of the treatment period.

1c. Neurological evaluations: Functional observation battery occurred during weeks 13 of the treatment period and week 19 of the recovery period.

2. Body weight: Animals were weighed once in the acclimatization period, twice weekly from weeks 1-4, then weekly.

3. Food consumption and compound intake: Food consumption was recorded once in the acclimatization period, twice weekly from weeks 1-4, then weekly. Food consumption for each animal was determined and mean daily diet consumption was calculated as g food/kg body weight/day. Compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the consumption and body weight gain data.

4. Ophthalmoscopic examination: Investigations were performed on all animals pre-treatment and on all control and high dose animals at weeks 13 and 19.

5. Hematology and clinical chemistry: Blood samples were drawn from all animals in weeks 13 and 19 from the retro orbital plexus under light isoflurane anesthesia, following approximately 18 hours fasting during urine collection. The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
X	Blood clotting measurements*		
X	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

b. Clinical chemistry:

X	ELECTROLYTES	X	OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes eg., *)	X	Total bilirubin
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase	X	Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/also SGPT)*		
X	Aspartate aminotransferase (AST/also SGOT)*		
	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

6. Urinalysis*: Urine samples were collected in weeks 13 and 19 from all animals. Urine was collected for an 18-hour period overnight. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose
X	Volume*	X	Ketones
X	Specific gravity/osmolality*	X	Bilirubin
X	pH*	X	Blood/blood cells*
X	Sediment (microscopic)	X	Nitrate
X	Protein*	X	Urobilinogen

* Optional for 90-day oral rodent studies

7. Sacrifice and pathology: All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	XX	Thymus*+	X	**GLANDULAR**
X	Ileum*			XX	Adrenal gland*+
X	Cecum*	X	**UROGENITAL**	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroid*
X	Rectum*	X	Urinary bladder*	XX	Thyroid*
XX	Liver*+	XX	Testes*+	X	**OTHER**
	Gall bladder (not rat)*	XX	Epididymides*+	X	Bone (sternum and/or femur)
X	Bile duct (rat)	XX	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin*
X	**RESPIRATORY**	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	XX	Uterus*+		
XX	Lung*	X	Mammary gland*		
X	Nose*				
X	Pharynx*				
X	Larynx*				

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
+ Organ weights required for rodent studies.

II. RESULTS:

A. OBSERVATIONS:

1. Clinical signs of toxicity: No treatment-related clinical signs were found.

2. Mortality: No unscheduled mortality occurred; all animals survived until scheduled termination.

3. Neurological evaluations: No treatment-related clinical signs or changes in motor activity were observed in either sex. A significant decrease (-22%, $p<0.05$) in forelimb grip strength was reported in the high-dose males. However, no dose response was evident and the value was reported to be within the historical control range for the laboratory (0.89 ± 0.31)[2]. A significant decrease (-16%, $p<0.05$) was reported in hindlimb grip strength in the high-dose recovery females. This effect was not considered to be treatment-related as no effects occurred during the treatment period.

B. BODY WEIGHT AND WEIGHT GAIN:

Bodyweight and bodyweight gain were impaired among males and females administered 3000 or 6000 ppm (Table 2). At the high dose, this was shown to be reversible during the recovery period (i.e. weight gain of rats previously impaired, was slightly improved over time).

2) Historical control data found on page 579 of the study report.

TABLE 2. Average body weights and body weight gains during 90 days of treatment [a]

Dose (ppm)	Body weights (g±SD)				Total weight gain (Days 1-91)	
	Week -1	Day 1	Day 29	Day 91	g	% of control
Male						
0	106.8 ± 5.2	154.8 ± 7.2	311.3 ± 17.9	435.7 ± 36.0	280.2	-
300	109.8 ± 4.9	158.2 ± 7.7	312.9 ± 27.1	436.0 ± 43.3	277.8	99.1
1000	107.4 ± 4.4	156.1 ± 5.8	300.2 ± 20.5	418.8 ± 39.0	262.7	93.8
3000	108.5 ± 5.9	154.6 ± 11.3	276.1 ± 24.3**	372.8 ± 36.7** (-14.4%)	218.2	77.9
6000	108.1 ± 4.8	158.8 ± 6.8	285.5 ± 15.0**	377.8 ±24.7** (-13.3%)	219	78.2
Female						
0	92.4 ± 4.3	127.2 ± 6.3	199.4 ± 12.0	259.3 ± 14.8	132.1	-
300	94.7 ± 4.4	128.5 ± 5.1	192.3 ± 11.4	249.3 ± 19.8	120.8	91.4
1000	94.9 ± 4.4	127.7 ± 6.2	193.2 ± 11.1	243.5 ± 19.1	115.8	87.7
3000	92.8 ± 3.6	125.2 ± 5.0	184.7 ± 11.5**	231.1 ± 17.6** (-10.9%)	105.9	80.2
6000	93.6 ± 3.9	128.8 ± 5.4	192.0 ± 12.0	235.5 ± 19.3** (-9.2%)	106.7	80.8
Male Recovery						
	Day 1	**Day 15**	**Day 29**	**Day 42**	(Recovery Days 1-42)	
0	444.9 ± 29.6	460.4 ± 28.5	487.9 ± 31.9	504.1 ± 35.9	59.2	-
6000	357.1 ± 29.5** (-19.7%)	390.7 ± 37.3** (-15.54%)	418.0 ± 42.5** (-14.3%)	431.7 ± 45.9* (-14.4%)	74.6	126
Female Recovery						
	Day 1	**Day 15**	**Day 29**	**Day 42**		
0	261.8 ± 8.0	279.1 ± 9.1	287.8 ± 14.2	288.0 ± 13.6	26.2	-
6000	220.3 ± 16.5** (-15.9%)	239.9 ± 12.5** (-14.1%)	244.9 ± 18.8** (-14.9%)	249.5 ± 17.5** (-13.4%)	29.2	111

[a] Data obtained from page 157-164 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Food consumption was not considered to be affected by treatment. During the initial 4 days of exposure, transiently lower food consumption was recorded for males and females offered 1000, 3000 or 6000 ppm. However, this was likely due to palatability.

2. **Compound consumption:** (time-weighted average) – Compound consumption was

calculated and reported in Table 1 above.

3. Food efficiency: Food efficiency was not reported.

D. OPHTHALMOSCOPIC EXAMINATION: There were no treatment-related changes in the eye.

E. BLOOD ANALYSES:

1. Hematology:

At week 13, male rats in the low and high-dose groups had slight but statistically significant increases in RBC counts. However, this value was reported as within the historical control range (7.98 to 9.78 T/l)[3]. Additionally, no dose-response relationship was established and no significant changes were reported in the recovery groups. Therefore, the increased RBC counts were not considered to be toxicologically relevant. Decreases in the MCV in the low- and high- dose groups and MCH in the high-dose groups were considered to be secondary to the increased RBC count and not a treatment-related effect. In females, a slight but statistically significant decrease in hemoglobin and decreased PTT were reported at 3000 and 6000 ppm, along with slightly decreased MCV and MCH in the high-dose group. Additionally, increases in lymphocytes and large unstained cells (LUC) were reported in the high-dose group. Reticulocytes were increased at 3000 and 6000 ppm in males, and 6000 ppm in females. All hematological findings recovered following the 6-week recovery period. Hematological changes at 3,000 ppm were not considered to be toxicologically relevant as no corresponding toxicity was observed and all effects were fully reversible following the recovery period.

3) Historical control data found on page 588 of the study report.

TABLE 3. Selected hematology parameters from rats treated for 90 days

Parameter	Dose level (ppm)				
	0	300	1000	3000	6000
Males					
RBC (T/l)	8.87	9.28* (+4.6%)	9.10	9.14	9.36** (+5.5%)
MCV (fL)	50.6	49.1* (-3.0%)	49.7	49.7	47.7** (-5.7%)
MCH (fmol)	1.10	1.06	1.08	1.07	1.02** (-7.3%)
Reticulocytes (g/L)	162	179	179	206** (+27%)	216** (+33%)
Females					
HB (mmol/L)	9.5	9.5	9.5	9.2** (-3.2%)	9.2** (-3.2%)
MCV (fL)	51.8	52.3	52.1	50.6	50.2** (-3.1%)
MCH (fmol)	1.14	1.15	1.14	1.11	1.10* (-3.5%)
Reticulocytes (g/L)	157	148	155	175	186* (+18.4%)
Lymph (g/L)	3.19	3.11	3.26	3.38	4.02* (+26%)
LUC (g/L)	0.05	0.06	0.06	0.06	0.07* (+40%)
PTT (sec)	29.8	31.0	28.7	24.3** (-18.5%)	22.0** (-26.2%)

Data taken from pp. 185-188, MRID 49020006.
[a] Reported as Mean, with n=12 for all groups.
* Significantly different ($p<0.05$) from the control.
** Significantly different ($p<0.01$) from the control.
Numbers in parentheses equal percent change, relative to control value, calculated by reviewer.

2. Clinical chemistry:

Treatment-related increases of total plasma cholesterol and phospholipids were found in males and females treated at 1000, 3000 and 6000 ppm, and triglycerides were increased in males and females at 6000 ppm. An increase in GGT was seen in males and females at 3000 and 6000 ppm. Total protein content and alpha-2 globulin fraction were increased in males at 1000, 3000 and 6000 ppm. Albumin was increased in males and females at 3000 and 6000 ppm, Alanine aminotransferase (ALT) was minimally increased in females at 6000 ppm

Other changes, including apparently marked increases in several electrolytes (primarily sodium, chloride, calcium and inorganic phosphate) seen at 3000 and 6000 ppm (but also involving the 1000 ppm dose level in some cases) were not considered toxicologically meaningful. With particular respect to electrolytes this conclusion was due to the absence of corroborating change in urinalysis, or of kidney histological change. Values remained within the historical control range (historical control data provided on page 590 of the study report).

At the end of the 6 weeks recovery period, all of the findings described above had steadily recovered.

TABLE 4. Selected clinical chemistry parameters from rats treated for 90 days with and without a 6-week recovery

Parameter	Dose level (ppm)				
	0	300	1000	3000	6000
Males					
Creatinine (µmol/L)	31.4	28.1* (-11%)	30.1	28.2* (-10%)	25.4** (-19%)
Cholesterol (mmol/L)	1.98	2.21	2.88** (+45%)	3.99** (+102%)	6.26** (+216%)
Triglycerides (mmol/L)	0.40	0.42	0.36	0.48	1.04** (+160%)
Phospholipids (mmol/L)	1.64	1.82	2.18* (33%)	2.97** (+81%)	4.54** (+177%)
GGT (U/L)	0.0	0.0	0.0	7.7**	19.5**
Sodium (mmol/L)	146.4	146.8	147.8	149.2** (+2%)	148.6** (+1.5%)
Phosphorus(mmol/L)	1.65	1.68	1.77* (+7.2%)	1.92** (+16%)	2.02** (+22%)
Protein(g/L)	71.28	71.95	74.18* (+3.6%)	76.58** (+7.4%)	81.44** +14%)
Albumin (g/L)	35.65	35.10	36.04	38.23** (+7.2%)	42.38** (+19%)
α-2 globulin (g/L)	5.62	6.18	6.44* (+15%)	7.18** (28%)	8.06** (+43%)
Males-Recovery					
Creatinine (µmol/L)	30.8	-	-	-	28.1* (-8.8%)
Cholesterol (mmol/L)	1.75	-	-	-	2.31* (+32%)
Phosphorus(mmol/L)	1.81	-	-	-	1.96* (+8.2%)
Females					
Cholesterol (mmol/L)	1.53	1.91	2.30** (+50%)	2.85** (+86%)	3.52** (+130%)
Triglycerides (mmol/L)	0.31	0.29	0.33	0.37	0.52** (+68%)
Phospholipids (mmol/L)	1.73	1.99	2.31** (+34%)	2.72** (+57%)	3.31** (+91%)
ALT (U/L)	27.9	24.4	24.6	25.9	36.9** (+32%)
GGT (U/L)	0.0	0.0	0.0	4.3**	19.1**
Sodium (mmol/L)	144.7	145.0	146.1** (+1%)	147.3** (+1.7%)	147.8** (+2.1%)
Chloride (mmol/L)	106.6	106.4	107.5	108.4** (+1.6%)	108.4** (+1.6%)
Calcium (mmol/L)	2.67	2.65	2.69	2.70	2.76* (+3.3%)
Albumin (g/L)	43.86	44.79	44.19	46.82* (+6.7%)	46.66* (+6.4%)
α-1-Globulin (g/L)	12.53	12.16	12.41	11.14** (-11%)	10.75** (-14%)
Females-Recovery					
α-1-Globulin (g/L)	10.94	-	-	-	11.84* (+8.2%)

Data taken from pp. 191-194, MRID 49020006.
[a] Reported as Mean, with n=12 for all groups.
* Significantly different ($p<0.05$) from the control.
** Significantly different ($p<0.01$) from the control.
Numbers in parentheses equal percent change, relative to control value, calculated by reviewer.

F. URINALYSIS:

Significant increases in leukocytes were observed in males at 6000 ppm ($p<0.005$) and females at 3000 and 6000 ppm ($p<0.01$). Increased leukocytes were not considered to be toxicologically relevant as no corresponding parameters were affected, and there were no effects on kidney weights or kidney histopathology.

TABLE 5. Selected urinalysis parameters from rats treated for 90 days

Parameter	Dose level (ppm)				
	0	300	1000	3000	6000
Males					
Leukocytes (per µL)	25	25	63	25	100* (300%)
Females					
Leukocytes (per µL)	0	0	0	25**	25**

Data taken from pp.197-198, MRID 49020006.
[a] Reported as Mean, with n=12 for all groups.
* Significantly different ($p<0.05$) from the control.
** Significantly different ($p<0.01$) from the control.
Numbers in parentheses equal percent change, relative to control value, calculated by reviewer.

G. SACRIFICE AND PATHOLOGY:

1. Organ weight:

Mean liver weights were significantly increased in males at 3000 and 6000 ppm by 25%, and 57%, respectively, and in females at 6000 ppm by 37% (Table 6). Relative liver weights were significantly increased in males at 3000 and 6000 ppm by 44%, and 78%, respectively, and in females at 3000 and 6000 ppm by 27% and 46%, respectively. All other findings were considered to be unrelated to treatment with the test item.

TABLE 6. Organ weight data from rats treated for 90 days

Parameter	Dose level (ppm)				
	0	300	1000	3000	6000
Males					
Liver: Absolute weight (g)	11.47 ± 1.54	11.88 ± 1.79	12.75 ± 2.18	14.36 ± 2.53** (+25%)	18.05 ± 2.37** (+57%)
Relative weight (% BW)	2.80 ± 0.28	2.81 ± 0.26	3.14 ± 0.37	4.04 ± 0.60** (+44%)	4.99 ± 0.61** (+78%)
Females					
Liver: Absolute weight (g)	7.30 ± 0.84	6.87 ± 1.01	7.59 ± 1.02	8.43 ± 0.44	10.01 ± 1.84** (+37%)
Relative weight (% BW)	3.05 ± 0.25	2.91 ± 0.34	3.30 ± 0.36	3.87 ± 0.19** (+27%)	4.46 ± 0.54** (+46%)

Data taken from pp. 200-215, MRID 49020006.
Reported as Mean ± Standard Deviation, with n=12 for all groups.
** Statistically different ($p<0.01$) from the control.
Values in parentheses denote % difference from controls

2. Gross pathology:

The only macroscopic finding that was considered to be related to treatment was enlarged

liver, reported among males at 3000 and 6000 ppm.

3. Microscopic pathology:

In the liver, intracellular depositions of a brown pigment were seen among males and females receiving 1000, 3000 or 6000 ppm. Bile duct proliferation and minor degrees of diffuse hepatocellular hypertrophy were also observed in males at 3000 and 6000 ppm, and females at 6000 ppm. Brown pigment in the kidney and diffuse acinar hypertrophy in mandibular salivary glands were observed in a dose-dependent distribution at 3000 and 6000 ppm. Following the recovery period, 1 male animal was reported with bile duct proliferation and no evidence of hepatocellular hypertrophy was observed in either sex. Brownish pigment in the kidney and hypertrophy of the mandibular glands were not considered to be adverse as they were fully reversible and no effects were reported in the recovery group.

TABLE 7. Selected Microscopic Pathology for Rats after 13 weeks

Parameter	Dose level (ppm)				
	0	300	1000	3000	6000
Males					
Liver					
- Brownish Pigment	0/12	0/12	4/12*	9/12**	12/12**
- Hepatocellular Hypertrophy	0/12	0/12	0/12	9/12**	12/12**
- Bile Duct Proliferation	0/12	0/12	0/12	1/12	2/12
Kidneys					
- Brownish Pigment	0/12	0/12	0/12	4/12*	9/12**
Mandibular Glands					
- Acinar Hypertrophy	0/12	0/12	0/12	3/12	5/12*
Females					
Liver					
- Brownish Pigment	0/12	0/12	10/12**	11/12**	10/12**
- Hepatocellular Hypertrophy	0/12	0/12	0/12	3/12	7/12**
- Bile Duct Proliferation	0/12	0/12	0/12	0/12	3/12
Kidneys					
- Brownish Pigment	0/12	0/12	0/12	8/12**	12/12**
Mandibular Glands					
- Acinar Hypertrophy	0/12	0/12	0/12	2/12	5/12*

Data taken from pp., 61-62 MRID 49020006.
Reported as Mean ± Standard Deviation, with n=12 for all groups.
** Statistically different ($p < 0.01$) from the control.
Values in parentheses denote % difference from controls

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

The study author concluded that decreased body weight gains in females, an increased tendency of absolute and relative liver weights in males, histological findings in liver and related effects in males and females were observed at 1000 ppm whereas no test item-related effect was recorded in both sexes at 300 ppm. Therefore, the no-observed-adverse-effect level (NOAEL) and the no-observed- effect level (NOEL) for systemic toxicity associated with dietary S-1563 exposure is 300 ppm (corresponding to 23.0 mg/kg/day in males and 24.8 mg/kg/day in females).

B. REVIEWER COMMENTS:

Following 90-days of administration of S-1563 to Wistar rats, the liver was the primary target organ. Increases in lipids, proteins, and GGT were identified along with enlarged livers, increases in liver weights, diffuse hepatocellular hypertrophy and bile duct proliferation. The EPA considers the effects at 1,000 ppm to be reversible and below the dose leading to tumor production, and therefore a NOAEL.

The systemic toxicity LOAEL for this study is 3,000 ppm (223/236 mg/kg/day) based on decreased body weights, increases in liver enzyme activity, lipids, protein, liver weights, diffuse hepatocellular hypertrophy and bile duct proliferation. The systemic toxicity NOAEL is 1,000 ppm (76/82 mg/kg/day).

***Note: PMRA agrees with the study author and considers the decrease in body weight gain in females at 1000 ppm (76/82 mg/kg bw/day) to be toxicologically relevant. Therefore, the PMRA considers the NOAEL to be 23/25 mg/kg bw/day, and the LOAEL to be 76/82 mg/kg bw/day**.

C. STUDY DEFICIENCIES: Minor deficiency: Stability data not provided.